LETTERS TO THE EDITOR

Elevated Serum C-Reactive Protein Levels in Osteoarthritis

Sir—Despite histological evidence of synovitis in some osteoarthritis (OA) patients [1, 2], most of the established serum markers of systemic inflammation are usually within the normal range. C-Reactive protein (CRP) is recognized as one of the most sensitive measures of inflammation [3, 4], but the standard turbidimetric assay widely used in clinical practice has a lower detection limit of ∼10 mg/l. However, more sensitive assays showed that the upper limit of the normal range is only ∼1 mg/l [5]. Consequently, serum CRP levels which are up to 10 times normal remain undetected in standard assays. The present study was thus undertaken to determine whether serum CRP levels are raised in patients with OA as judged by a sensitive assay.

Sera from 167 members of a cohort [48 males and 119 females; mean (s.d.) age 65.0 (11.8) yr] of patients with OA of the knee [6] were used. Sera from 51 healthy volunteers [18 males and 33 females; age 35.5 (9.9) yr] who had no knee pain and no history or signs of joint disease nor of recurrent infections were used as controls. Serum CRP levels were measured by an automated PAMIA-30 counting immunoassay (TOA Medical Electronics Co. Ltd, Japan) with a lower detection limit of 0.02 mg/l [7]. Data were analysed following logarithmic transformation (natural log) to allow for their skewed distribution and presented as geometric means with 95% confidence intervals (CI). Between-group differences were compared using Student’s $t$-test and Spearman correlation was used for testing associations with age and gender.

The average intra-assay and inter-assay CVs of the PAMIA-30 counting immunoassay were 6.2 and 13.0%, respectively. Serum CRP concentrations are shown in Fig. 1. They were highly skewed in distribution, but normally distributed after logarithmic transformation. The geometric mean (95% CI) CRP concentration in patients with OA was 3.25 (2.59, 3.91) and that in normal controls was 0.93 (0.11, 1.75) mg/l (unpaired $t$-test; $P < 0.0001$). The patients with OA were older than controls and had a higher male to female ratio. However, no significant correlations were found with age ($r = 0.011$, 95% CI: $−0.271$, 0.291 for the control group and $r = 0.054$, 95% CI: $−0.102$, 0.207 for patients with OA) or sex [0.84 ($−0.36$, 2.03) in men and 0.99 ($−0.11$, 2.09) in women ($P = 0.386$) for the control group].

The results thus show that serum CRP concentrations are raised in many patients with established knee OA compared to healthy subjects. Since the values obtained for CRP levels in most of the OA patients and almost all of the normal individuals fall below those detectable by the standard turbidimetric assay, the difference between the controls and the OA patients may not be revealed by such assays. The modest rise in serum CRP levels in OA may relate to mild synovitis. However, we cannot entirely dismiss the possibility that the elderly OA patients have other intercurrent diseases which cause elevated CRP. CRP levels are regulated by cytokines, particularly interleukin-6, interleukin-1 and tumour necrosis factor-$\alpha$. These cytokines are produced locally in OA joints [8–11]. It would seem likely, therefore, that it is these cytokines which stimulate CRP production in OA. How synovial inflammation is involved in the pathogenesis of OA remains to be established. In rheumatoid arthritis, CRP concentrations correlate with synovitis, joint erosions and radiographic progression [12–14]. It will be important to determine whether elevated CRP correlates with the severity of radiographic features, particular constellations of clinical symptoms or evidence of disease progression in OA.

We acknowledge TOA Medical Electronics Co. Ltd, Japan, who supplied the PAMIA-30 system and all reagents. We thank Miss K. Meadows and Mr L. Shepstone for technical and statistical support.

![Fig. 1.—Serum C-reactive protein levels measured by a highly sensitive counting immunoassay (PAMIA-30) in normal subjects (controls) and patients with osteoarthritis (OA). The solid horizontal bars represent the absolute mean values in each group.](image-url)
HLA-DRB1* Genotypes in Greek Rheumatoid Arthritis Patients: Association with Disease Characteristics, Sex and Age at Onset

Sir—The association of certain HLA-DRB1* genotypes in Greek rheumatoid arthritis (RA) patients with disease characteristics, sex and age at onset was investigated. This study was designed because differences have been reported in the HLA-DR profile between Greek and northern European RA patients [1–4]. The study included 86 unrelated Greek RA patients (13 males, 73 females) fulfilling ACR criteria [5] and 130 controls matched to the cases by ethnic origin and age. The patients’ age ranged from 24 to 80 yr (mean 55.2 yr, s.d. 12.2). RA patients hospitalized (35%) or seen as out-patients (65%) in the rheumatology departments of two hospitals located in the Athens metropolitan area over a 1 yr period were asked to participate. No patient refused. HLA typing was performed by polymerase chain reaction (PCR) and SSO [6]. Mantel–Haenszel (M–H) (one-tail). Fisher’s exact and M–H for linear trend tests were used for statistical analyses [7].

The age at onset ranged from 23 to 80 yr (mean 48.9, s.d. 12.9); in 36.5%, it was below 45 yr. A total of 81% of patients had positive rheumatoid factor (RF) at some stage of the disease, 70% presented radiological erosions and 13% s.c. nodules. Felty’s syndrome was absent from all RA patients. Genotypes HLA-DR4 and DR10 were significantly increased among RA patients; 37.2% of these patients and 16.9% of controls were positive for DR4 (RR = 2.9, P < 0.001); 10.5% of patients and 4.6% of controls were positive for DR10 (RR = 2.4, P = 0.045). HLA-DR1 was increased (RR = 1.79), though not significantly, after controlling by stratification on DR4 and DR10. Stratification of genotypes into DRB1* alleles showed that *0101, *0401, *0405 and *1001 are associated with a statistically significantly (P < 0.01) elevated risk of developing RA (RR = 2.60, 13.23, 8.23 and 2.42, respectively). The *0408 allele was absent from RA patients, but present in 1.5% of controls. Alleles with the shared epitope (shared sequence of amino acids within the third hypervariable region of the HLA-DRB1* molecule [8, 9] SE) *0101, *0102, *0401, *0404, *0405, *0408, *1001 were present in 65% of cases vs 31.5% of controls (RR = 4.05, P < 0.00001). A total of 47.7% of cases and 28.5% of controls carried a single SE allele, whereas two SE alleles were present in 11.6% of the cases and 2.3% of the controls (P < 0.001). The presence of one SE allele led to a 2.85-fold increase in the risk for RA, when compared to the absence of both (SE−/SE−), whereas this increase was 8.57-fold when two SE alleles were present. Certain characteristics of a single SE+ were compared to the SE−/SE−. The largest significant effect was with *0401, followed by *0405 and *1001, with RR of 10.5, 9.43 and 2.40, respectively.

The risk of having positive RF and s.c. nodules was higher among subjects carrying two SE alleles: for RF RR = 9.13 (P < 0.001); for nodules RR = 10, but not significant. Most significant findings (P < 0.01) persisted after stratification by sex, despite the small number of male cases and corresponding limitations of power. Specifically, the RR for men was double the size of that for women in the single SE allele category (RRs 5.68 and 2.67, respectively) and four times higher in the presence of two SE alleles (RRs 30 and 7.74). Stratification by age at RA onset showed that men younger than 45 yr had a five times higher risk than women when they carried two SE alleles (RR = 60 vs 12, P < 0.01). Men older than 45 yr had a risk three times higher (but not significantly so) than women (15 vs 4.74). For the over 45 age group, the increase in risk for both sexes was significant in SE+/SE+ vs SE−/SE− (P < 0.004).
The results of this study indicate that the SE sequence, particularly on both haplotypes, predisposes to seropositive RA in the Greek population, as has been observed in northern Europeans [10]. In addition, SE alleles were positively associated with susceptibility at a young age, particularly in young men.

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Clubbing in Patients with Human Immunodeficiency Virus Infection

SIR—We read with great interest the paper by Boonen et al. in this journal [1]. We conclude that clubbing and HOA must be included in the wide spectrum of rheumatic manifestations in patients with HIV infection. Because of the high number of associated infections and neoplasms, the role of HIV in the development of clubbing and HOA is difficult to determine in these patients.
LETTERS TO THE EDITOR 143

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Reactive Arthritis in a Patient with Simultaneous Parvovirus B19 Infection and Clostridium difficile Diarrhoea

Sir—We report a case of Clostridium difficile diarrhoea and arthritis after antibiotic treatment for a skin infection. Retrospectively, parvovirus B19 (B19) was suggested as the cause of the primary infection.

A 34-yr-old woman was prescribed cefuroxime for impetigo, as diagnosed by a general practitioner. Diarrhoea and urticaria developed within a week; faecal culture of *Clostridium difficile* was positive. After another week, arthralgias, myalgias and iritis developed.

On admission to the hospital on 7 March 1993, arthritis of the right ankle joint and arthralgia of the wrists were observed. Walking was difficult, and the patient complained of mild dysuria. The blood haemoglobin was 103 g/l, the peripheral blood leucocyte count was normal (5.8 × 10⁹/l), but the C-reactive protein (CRP) level was high (126 mg/l). The axial temperature was 38.7°C. The urine sample revealed leucocytosis; the bacterial culture later proved negative. Ciprofloxacin was given i.v. for 3 days for suspected pyelonephritis. Metronidazole treatment started 4 days before hospitalization was also continued for 3 days. Synovial fluid examination revealed leucocytes 3750 × 10⁶/l with 42% mononuclear cells and 58% polymorphonuclear cells. The joint symptoms gradually subsided. However, the diarrhoea began again on 16 March, and with *C. difficile* positive in the stool sample, metronidazole was readministered. The diarrhoea and fever subsided in a week. Rheumatoid factor was negative. All five blood cultures taken during the hospitalization were negative. No serum antibodies to *Chlamydia trachomatis*, *Campylobacter*, *Salmonella* and *Yersinia* were detectable. The patient was discharged home symptom free on 30 March 1993. In the last control a year later, this HLA-B27-positive patient was healthy, except for occasional arthralgias of the ankle and knee joints.

A blood sample drawn on 11 March 1993 revealed, retrospectively, the presence of B19 DNA sequences, by using two B19-specific polymerase chain reaction (PCR) assays [1]. Circulating B19-specific IgM and IgG were also present in high concentrations. It seems apparent that our patient suffered initially from a B19 infection and subsequently developed *C. difficile* diarrhoea. The ‘impetigo’ was probably a rash caused by B19.

The clinical picture of the arthritis fits with *C. difficile* reactive arthritis (ReA). On the other hand, a typical Reiter’s syndrome in association with B19 infection has been reported [2], and our patient had arthritis, iritis and urethritis. It is not possible to distinguish, by clinical or other criteria, whether she had a B19 arthritis or *C. difficile*-associated arthritis, or both. *Clostridium difficile*-triggered ReA seems to be associated with HLA-B27; 12 (63%) of the 19 B27-typed cases published have been B27 positive [3–10].

In several previous reports of ReA associated with *C. difficile* diarrhoea, the primary symptoms are typical for respiratory infections. Paty and Nichols [3] reported a pregnant woman with a flu-like illness and pruritic skin rash occurring before *C. difficile*-associated arthritis. Of the three patients reported by Hannonen *et al* [5], one had an upper respiratory infection and one had acute tonsillitis as the primary infection. A navy sailor reported by Keating and Vyas [10] suffered primarily from sinusitis. In two other reports, *C. difficile*-associated arthritis was preceded by insect bites [4, 6]. The lack of microbiological diagnosis of the primary infection is common to all these cases; therefore, the possibility that the arthritis was due to the primary infection cannot be ruled out.

We conclude that the aetiopathogenesis of *C. difficile*-associated ReA should be studied more extensively. Finding bacterial antigens or bacterial DNA in the inflamed joint would give more evidence of the true arthritogenic nature of *C. difficile*. It is possible that the development of ReA is only indirectly caused by *C. difficile*, by inducing a change in the intestinal flora, a situation resembling ReA developing after intestinal by-pass. However, even in such a case, the bacterial antigens or DNA should occur in the joint tissue. Likewise, the role of B19 and other arthritogenic microbes causing the primary infection should be taken into account.

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Effective Treatment of Anti Jo-1 Antibody-Positive Polymyositis with Cyclosporin

Sir—We read with interest the letter from Tellus and Buchanan [1] on the treatment of Jo-1 antibody-positive polymyositis with cyclosporin. Currently, we are treating a patient with Jo-1 antibody-positive polymyositis, similarly in whom remission was induced eventually with prednisolone and cyclosporin. In contrast to the case described, our patient has not been satisfactorily maintained in remission on this regimen.

In 1993, Mrs SM, a 31-yr-old nurse, presented 2 months postpartum with a seronegative inflammatory polyarthritis affecting the wrists, knees, ankles and small joints of the hands and feet. Examination revealed, in addition to synovitis, that she had fine inspiratory crackles at her lung bases and proximal muscle weakness. Investigations showed creatinine phosphokinase (CPK) of 7815 IU/l (normal 23–150 IU/l) and aldolase of 296 IU/l (0–7.5 IU/l); electromyography studies confirmed acute polymyositis. Autoantibodies and rheumatoid factor were negative. Anti Jo-1 antibodies were positive. Haemoglobin was 11.2 g/dl with normal indices and plasma viscosity was normal. C-reactive protein was normal. Pulmonary function tests showed a restrictive ventilatory pattern [forced expiratory volume in 1 s (FEV1) 2.27 l, FEV1/FVC 85%] and reduced carbon monoxide transfer factor 4.7 mmol/kPa·min. She was then treated with oral prednisolone 60 mg (1 mg/kg/day) and cyclosporin 150 mg/day (2.5 mg/kg/day). To maintain disease control and facilitate prednisolone reduction, cyclosporin was gradually increased. Prednisolone was reduced by 10 mg/month to 40 mg/day, then by 5 mg/month to 20 mg/day with a plan to reduce by 2.5 mg/month thereafter. At a dosage of 17.5 mg of prednisolone and 225 mg of cyclosporin, her disease flared (CPK 1345 U/l) and so prednisolone was increased to 30 mg/day and cyclosporin up to 250 mg/day. Symptoms and CPK levels improved, and prednisolone was reduced over 6 weeks to 20 mg and then reduced by 2.5 mg/month. On 15 mg/day of prednisolone, she was asymptomatic and the CPK level was normal. At 12.5 mg/day of prednisolone, CPK started to rise, so cyclosporin was increased up to 275 mg/day and prednisolone back to 15 mg/day. After 3 months of this dosage of cyclosporin, serum creatinine levels were 30% above baseline and the dosage of cyclosporin had to be reduced, which resulted in increasing muscle enzyme levels and an increase of prednisolone dosage to 20 mg/day to control the disease. Currently, pulmonary function tests are FVC 3.19 l (90% of predicted), FEV1 2.27 l, transfer factor 4.7 mmol/kPa·min. We support the suggestion that cyclosporin is a useful therapeutic option in inducing remission in Jo-1 antibody-positive polymyositis. The time to remission was significantly longer than in Tellus and Buchanan’s case report, and relapses occurred, necessitating increasing doses of cyclosporin which resulted in renal dysfunction. Clearly, a formal prospective trial of cyclosporin in relapsing polymyositis is needed with
at least 1 yr follow-up after remission has been produced.

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Accepted 20 June 1996


**NSAIDs and Fertility**

Sir—I read with interest the case report of Akil et al. [1] regarding a possible association between non-steroidal anti-inflammatory (NSAID) drug use and anovulation, which the authors suggested may have resulted from the luteinized unruptured follicle syndrome (LUF).

Edinburgh researchers recently monitored three ovarian cycles among three patients with inflammatory arthritis [2]. These women used unspecified NSAIDs during two cycles and discontinued the NSAIDs over the periovulatory period during the third cycle. Baseline serum luteinizing hormone (LH), follicle-stimulating hormone (FSH) and oestradiol levels were taken to exclude other ovulatory distortions. Urine samples were monitored for oestrone, LH and pregnanediol as ovulation markers. From day 10 until (a) ovulation or (b) a LUF was diagnosed, daily transvaginal ultrasound scans were performed, and serum oestradiol and LH were measured. In all three cases, NSAID therapy was associated with LUF, except for the third cycle where normal ovulation occurred following drug withdrawal.

Prostaglandin inhibitors are frequently prescribed for women suffering with endometriotic pain [3], although clinical trials using NSAIDs for endometriotic symptom relief have not been overly impressive [4]. A small clinical trial did, however, find naproxen more successful than placebo in relieving endometriotic pelvic pain [5]. Unlike primary dysmenorrhea, where the pain often begins immediately before or at menses onset and is gone within 48 h, dysmenorrheic endometriosis pain may start several days before and persist throughout the menses and even a few days thereafter [6]. As endometriosis progresses, pain can extend over the entire luteal phase, leaving only a few pain-free days post-menstrually [6]. The dyspareunia experienced by many women with endometriosis is often more painful in the peri-menstrual phase [7]. A sonographic study of uterine contractions among non-pregnant women noted that women with endometriosis experienced significantly increased uterine peristalsis during the early and midfolllicular phases [8]. Therefore, it is entirely possible that women with endometriosis use NSAIDs, intermittently, at varied menstrual cycle phases, based upon their symptoms—including the periovulatory phase.

Although the majority of research on endometriosis has focused on infertility over the last 60 yr, the association of infertility with endometriosis remains unclear. Certainly, the anatomic distortion secondary to invasive endometriosis and related adhesions is a well-understood deterrent to fertility. However, the lower fecundity rates of endometriotic women with mild endometriosis indicates that endometriosis per se may not be a direct cause of infertility and that infertility experienced by women with mild endometriosis should be considered ‘unexplained’ [7].

The capacity of endometriotic implants to synthesize prostaglandin F (PGF) has been demonstrated [9]. Alterations in fallopian tube prostaglandin production have been noted among endometriotic women [10]. Several researchers have reported increased levels of PGs in peritoneal fluid among endometriotic women [11, 12] and in endometriotic tissue [13].

Lastly, a recent study among six healthy women found that 50 mg indomethacin three times a day over the periovulatory period can delay follicular rupture—in five of six women from 2 to 12 days—with a reduction in intrafollicular blood flow, and without any apparent effect on hormonal and menstrual status [14].

While Akil et al. [1] wish to alert their fellow rheumatologists to this potential NSAID impact among childbearing women wishing to conceive, I would further suggest that all practising clinicians, including family practitioners, gynaecologists and endocrinologists, need to be more cognizant of this phenomenon.

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Accepted 16 May 1996

11. Drake TS, O’Brien WF, Ramwell PW, Metz SA. Peritoneal fluid

Reply
Sir—We agree with Thylan that the possible effect of NSAIDs on fertility deserves wider appreciation and note that our report has been supported by Roberts et al. [1], in an article of which we were not aware when submitting our paper.

The thrust of Thylan’s letter seems to be that NSAIDs may be responsible for some of the infertility associated with endometriosis. This may or may not be the case, but we agree that an assessment of infertility should now include obtaining a history of the use of NSAIDs and who may not yet be contemplating a pregnancy.

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Re: Measuring Outcomes in Rheumatoid Arthritis—Which Measures are Suitable for Routine Use?
Sir—I note Professor Blake’s comments with interest and agree that there is considerable scope for debate on whether we should measure outcomes and, if so, which outcomes, how we should measure outcomes and how frequently. Professor Blake rightly suggests that we may shoot ourselves in the foot if all we do is record deterioration.

We do in fact already record outcomes, but poorly and in an unrepeatable and usually non-quantitative way. At the crudest level, we record in the notes ‘patient better, same or worse than last time’. The problem with this method, and this is essentially I think what Professor Blake is suggesting, is that it is unreliable, unquantifiable and fails most tests of validity. I agree with him that we must capture the impact of clinical events and the effect of our therapy—the question is how can this be done without simply recording gradual deterioration over time?

Part of the answer, but not the whole answer, is to use an instrument which measures health-related Quality of Life (HR-QOL) [1]. This allows one to avoid the trap of comparing the patient with external criteria, against which they will inevitably fail, and allows one to measure the patient against their own standards, which adapt with age and duration of disease. The task then is to demonstrate (using a valid and reliable instrument) that over the lifetime of the patient we improve QOL when things go wrong and that the area under the QOL curve over time is maximized for as long as possible.

There are candidate instruments for achieving this [2]. For example, we have undertaken a large study comparing the performance of ACR disease activity measures with two generic measures—the MOS-SF36 and EuroQol [3]—which will shortly be submitted for publication. One of our main conclusions, however, is that EuroQol, which can be used either as a very simple health profile or as a health index, is valid, more sensitive to change than most of the ACR measures and is reliable (Table I) on test–retest over 3 months. EuroQol satisfies the basic requirements of an HR-QOL instrument [1], is very simple to use and is a candidate instrument for routine clinical use—it could certainly be used on multiple and frequent occasions.

In conclusion, Professor Blake is only partly right; although more work is still needed, simple instruments like EuroQol are candidates for routine use. We will shortly be trialling it in routine practice. The debate should continue.

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Accepted 12 June 1996

TABLE I
Standardized response means (SRM) for EuroQol and disease-specific measures in patients (n = 56) reporting improvement over 3 months

<table>
<thead>
<tr>
<th>Measure</th>
<th>SRM (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease activity—doctor</td>
<td>1.0</td>
</tr>
<tr>
<td>Pain VA scale (10 cm)</td>
<td>0.85</td>
</tr>
<tr>
<td>EuroQol—thermometer</td>
<td>0.75</td>
</tr>
<tr>
<td>EuroQol—utility</td>
<td>0.71</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>0.64</td>
</tr>
<tr>
<td>Joint tenderness</td>
<td>0.59</td>
</tr>
<tr>
<td>Disease activity—patient</td>
<td>0.5</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.4</td>
</tr>
<tr>
<td>ESR</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Reliability coefficients (RC) for each instrument in patients (n = 89) reporting no change in RA over 3 months

<table>
<thead>
<tr>
<th>Measure</th>
<th>RC (95% CI*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAQ</td>
<td>0.9 (0.8–1.0)</td>
</tr>
<tr>
<td>EuroQol—thermometer</td>
<td>0.61 (0.51–0.71)</td>
</tr>
<tr>
<td>EuroQol—utility</td>
<td>0.55 (0.45–0.65)</td>
</tr>
<tr>
<td>VA pain scale</td>
<td>0.5 (0.4–0.6)</td>
</tr>
<tr>
<td>Tender joint score</td>
<td>0.48 (0.38–0.58)</td>
</tr>
<tr>
<td>Disease activity—patient</td>
<td>0.42 (0.32–0.52)</td>
</tr>
<tr>
<td>Swollen joint score</td>
<td>0.35 (0.25–0.45)</td>
</tr>
<tr>
<td>Disease activity—physician</td>
<td>0.34 (0.24–0.44)</td>
</tr>
</tbody>
</table>

Let us not forget that QOL measures are being used to assess QoL for clinical purposes. The definition of QOL is important. The underlying assumption in arguing for using individualized weightings when assessing QoL to be poor. With time and adaptation to new circumstances, such individuals may again find fulfillment and an improved QOL even though the impairment and disability remain. There are instruments such as EuroQol and SEIQoL, which to some extent satisfy this definition.

I agree that the question of whose weightings should be used in such instruments is important. While the notion of using the subject’s valuations is attractive, it must not be forgotten that QOL measures are being incorporated into decisions on resource allocation, and it is society as a whole which pays for the resources, not the individual subject. Thus, there is a political dimension which cannot be ignored and there are dangers in taking too subjective a view of health.

May I also point out one or two errors of fact in Carr’s article? They refer to the standard gamble (SG), time trade off (TTO) and quality of life adjusted years (QALY) as being of use in cost–benefit analysis (CBA). This is not correct and may cause some confusion to the uninitiated. CBA explicitly compares the cost of treatment with the benefit of treatment measured in monetary terms rather than in units of health. SG and TTO are used to derive a ‘utility’ for use in calculating a QALY in cost–utility analysis (CUA). The EuroQol and Quality of Wellbeing scale to which they refer also provide a ‘utility’ value for CUA, and the EuroQol has a set of weightings which were obtained by using TTO in a population survey [3]. It is important to appreciate the methodological relationships between SG, TTO and QOL instruments such as EuroQol.

Finally, Carr et al. have omitted to mention one crucial difference between health profiles and utility-based measures such as health indices, TTO etc. Utility-based measures explicitly value death and perfect health as 0 and 1 respectively, providing anchor points for their scales, whereas profiles do not and are therefore limited in their application.

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Accepted 12 June 1996


Reply

Sir—Dr Hurst raises some interesting issues in response to our review of Quality of Life (QoL) measures.

He suggests that Calman’s [1] definition of quality of life as ‘the extent to which an individual’s hopes and expectations are matched and fulfilled by experience’ should be adopted as the operational definition of QoL. This is an interesting definition, implying, as we have argued, that quality of life should be judged by the individual rather than health professionals or society.

Indeed, use of this definition would strengthen the argument for using individualized weightings when assessing QoL for clinical purposes.

Where QoL assessments are incorporated into decisions about resource allocation, we acknowledge the political dimension of such decisions and the need to take a more objective overview of health and need, but would still argue that the individual’s weightings are important. The underlying assumption in arguments against using individualized weightings in...
resource allocation seems to be that subjective views of health/illness will necessarily result in demands for more resources. We would and have [2] argued that the converse may occur. Consider Dr Hurst’s example of a disabled individual who has adapted to using a wheelchair and rates his/her quality of life as excellent. Society’s assessment of that individual’s quality of life, based on what is considered to be ‘normal’ and/or desirable for someone of the same age, would be much lower than the individual’s. Resource allocation, based on society’s weightings, might involve the provision of resources aimed at increasing mobility, e.g. surgery, physiotherapy, extra aids, specially adapted vehicles and so on, for a patient who does not want such interventions. Anecdotal reports of the number of Zimmer frames used as clothes horses, rather than mobility aids, provide some evidence that inappropriate allocation of resources based on a desire to return patients to a society-defined norm does occur in practice.

Adoption of Calman’s definition would help to clarify the classification of various health status measures, some of which are described as QoL measures. Use of such a definition would make inclusion of patient preferences and aspirations a prerequisite for QoL measures. Thus, of the existing measures discussed in the review, only the SEIQoL could claim to be a measure of general health-related QoL. The MACTAR would qualify as a measure of QoL related to physical and social function. The Disease Repercussion Profile measures patient-perceived handicap, a concept similar to the negative dimension of Calman’s definition, i.e. the disparity between an individual’s preferences or aspirations and their experience which is due to disease.

In response to Dr Hurst’s point about the econometric methods of assessing QoL, we accept the criticism that use of the term cost–benefit analyses may have been misleading. We are aware of the distinctions between cost–effectiveness, cost–benefit and cost–utility analyses and issues relating to the use of health indices such as the EUROQoL in cost–utility analyses, but felt that this complex area would be better dealt with in a review of health economic analysis. Indeed, Dr Hurst’s final point highlights the complexity of this area.

He lists one of the benefits which utility-based measures (including health indices) have over health profiles as being the scale anchors of death and perfect health. Whilst a number of health indices and econometric methods (e.g. the Rosser Index [3] and the Quality of Well-being Scale [4]) do include these anchors, others do not. The descriptive sections of the EUROQoL, for example, which is recommended for use in clinical trials [5], measures self-rated health status on a continuum between the worst and best imaginable health states. Death as an anchor is only introduced in the version of the instrument specifically intended for use in the valuation of different health states.

In those instruments which do include death as an anchor, the problem arises of how to deal with those health states which are rated as worse than death. Instruments either rate these as the same as death, i.e. 0, the ‘zero option’ [6], thus biasing the valuation of health states, or assign negative values. Assigning negative values results in scales that are negatively skewed and asymmetric, and for which there is disagreement about the best method of analysis [7].

The inclusion of death and perfect health as anchors for scales which are used to value different health states in economic analyses is intuitively attractive as it facilitates the mathematical manipulation of comparative data. However, where the object of measuring QoL is to identify problems in clinical practice or to assess the effectiveness of different interventions on a number of dimensions of individuals’ lives, such anchors are not necessary. In this situation, measures which reflect the multidimensionality of quality of life, such as health profiles, are preferable to those which combine its various components to produce a single score (health indices) in a way which obscures the different weights which individuals attach to those components. Thus, whilst health indices may have an advantage over health profiles in economic analyses, health profiles are more useful in clinical situations to describe the impact of disease and/or treatment.

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Pulmonary Toxicity, Methotrexate and X-Rays

Sir—I read with interest Beyeler et al.’s [1] excellent study addressing the problem of pulmonary toxicity with methotrexate. The authors conclude that routine assessment of pulmonary function is unhelpful. I was a little disappointed that they did not comment on the value of routine chest radiographs since Drs Richards and Helliwell, in recent correspondence, appear to agree with BSR guidelines which suggest that a pre-treatment chest radiograph in patients commencing methotrexate is of value [2, 3]. I am not at all convinced of this and the study of Beyeler et al.
suggests that a more selective approach is indicated. The argument in favour of pre-treatment radiographs is, I assume, that it is necessary to document existing abnormalities so that, if respiratory difficulties arise in the future, the availability of previous films aids in assessment. There is no evidence to support this contention and there is no justification for the practice of routinely obtaining baseline chest films [4]. If the BSR guidelines are applied universally, a large number of individuals with no respiratory symptoms and signs will have chest radiographs. Further, the concern that routine pre-treatment chest radiographs are being used as a substitute for thorough clinical evaluation must be a real one. I fear that this practice reflects defensive medicine rather than evidence-based medicine.

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Reply
Sir—We thank Dr Jobanputra for his valuable comments.

The aim of our study was to assess lung volumes and gas exchange during methotrexate (MTX) treatment and not to analyse the value of routine chest X-rays before MTX treatment. Within our study, chest X-rays were needed for the interpretation of changes in pulmonary function. However, in daily practice based on our clinical experience, we perform costly chest X-rays (before or during MTX treatment) only in case of a history of lung disease, the presence of respiratory symptoms or abnormal clinical signs. This approach demands a thorough patient history and careful clinical examination, and results in a small risk of missing a lung disease in an asymptomatic patient.

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Iliopsoas Bursa Enlargement
Sir—In the recent case report by Doctors Byrne, Rees and Williams [1], I was surprised to see that Fig. 4 has been reproduced from the paper by Meaney et al. [2] on iliopsoas bursa enlargement. This figure appears without acknowledgement. I was less surprised to see another case report on iliopsoas bursa enlargement so soon after the last one carried by your journal [3] in view of its underrecognition as a cause of hip pain and inguinal swellings. A colleague of mine who recently described another case found that several references did not appear on a Medline search. The apparent underreporting of this condition may therefore reflect, in part, a failure of indexing.

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Reply
Sir—Thank you for the opportunity of making the following reply.

We agree that it is important to emphasize the different modes of presentation and the diagnostic difficulties associated with this condition. Our case is unusual since the bursitis was the presenting feature of metastatic carcinoma. Permission to reproduce Fig. 4 was received, but unfortunately not acknowledged. In view of the comments on missing references, we conducted our own Medline search on Ovid CD and found the following.

Between 1992 and May 1996, five references were found with a textword search of ‘ilio psoas bursitis’. An extra three references were found with a textword search of ‘ilio psoas burs$’ (to include ‘itis’/’a’/’ae’) revealed an extra seven references. A subject heading search using the medical subject headings (MeSH) term ‘bursa’ (→synovial bursa) found an extra reference. Use of the subject heading ‘cyst’ (→synovial cyst) located an extra two references. (Between 1966 and May 1996, there are 23 references found as ‘ilio psoas bursitis’ (textword) and yet only three of these are MeSH indexed as ‘synovial cyst’.)

We feel this example illustrates well the problems associated with Medline indexing and searching, which are not well appreciated [1]. There is a case to be made for researchers quoting the method of searching and specifying, e.g. which database, which CD Rom, which textwords, and which subject headings were used.

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